1 545 767

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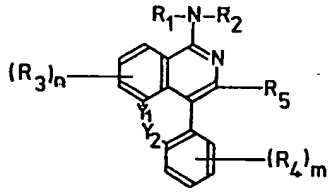
(54) ISOQUINOLINE DERIVATIVES

(71) We, ASPRO-NICHOLAS LIMITED, a British Company of 225 Bath Road, Slough SL1 4AU, England, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to compounds having an isoquinoline nucleus and provides certain 1-amino-4-phenyl-isoquinolines and methods for their preparation. The invention provides also pharmaceutical compositions containing said compounds.

According to the present invention, there are provided 1-amino-4-phenyl isoquinolines of formula II:—



II

wherein R_1 and R_2 independently represent hydrogen or C_1—C_{12} alkyl, preferably C_1—C_4 alkyl, or R_1 and R_2 together with the amino nitrogen atom represent a piperazinyl ring optionally substituted by C_1—C_{12}, preferably C_1—C_4 alkyl or C_1—C_{12}; preferably C_1—C_4 hydroxyalkyl;

n represents zero or an integer not exceeding 3, preferably 0 or 1;

m represents zero or an integer not exceeding 4, preferably 0 or 1;

R_3 and R_4 independently represent C_1—C_{12} alkyl, preferably C_1—C_4 alkyl, optionally substituted by one or more halogens; C_1—C_{12} alkoxy, preferably C_1—C_4 alkoxy or halogen;

R_5 represents hydrogen or C_1—C_{12} alkyl, preferably C_1—C_4 alkyl; and

Y_1 and Y_2 independently represent hydrogen, C_1—C_{12} alkyl, preferably C_1—C_4 alkyl, C_1—C_{12} alkylthio, preferably C_1—C_4 alkylthio, C_1—C_{12} alkoxy, preferably C_1—C_4 alkoxy, or Y_1 and Y_2 together represent a single valency bond, an oxygen or sulphur atom or an alkylene radical optionally containing one or more oxygen or sulphur atoms and joining the 4-phenyl group to the isoquinoline nucleus in a chain of 1 to 3 atoms, the acid addition and quaternary ammonium salts thereof.

Examples of suitable R_1 and R_2 groups are hydrogen, methyl, and those divalent radicals which together with the amino nitrogen atom will form a 4-X-substituted

piperazin-1-yl group wherein X represents hydrogen, C_1—C_4 alkyl, e.g. methyl, or C_1—C_4 hydroxyalkyl, e.g. β-hydroxyethyl.

Examples of suitable R_3 and R_4 groups are methyl, trifluoromethyl, methoxy and chlorine.

Examples of suitable R_5 groups are hydrogen and methyl.

Examples of suitable Y_1 and Y_2 groups are hydrogen, methyl, methoxy, methylthio and, when Y_1 and Y_2 together represent an alkylene group, ethylene, methyleneoxy, methylenethio and isopropylidene. It will be appreciated that in the case where Y_1 and Y_2 together represent an unsymmetrical alkylene group such as methyleneoxy, there will be two possible isomers. In the particular case of methyleneoxy, one isomer has the oxygen atom attached to the 5-position of the isoquinoline ring and the other isomer has the oxygen atom attached to the 4-phenyl ring. Both of such isomers are intended unless specifically stated otherwise.

The presently preferred compounds of formula II are those in which R_1 represents methyl and R_2 represents hydrogen or methyl, especially those in which R_3 and R_4 independently represent chlorine or methoxy or *m* and/or *n* is zero.

Compounds of the present invention have been found to possess valuable pharmacological properties, in particular anti-inflammatory, especially anti-rheumatic, and/or C.N.S. activity, as determined by the rat paw volume test (modified version of that described by Winter *et al* in Proc. Soc. Exp. Biol. Med. 1962, III, 544) and by inter-action studies with amphetamine (see Quinton *et al*, Nature, 1963, Vol. 200, 178—9) respectively. The precise extent of pharmacological activity does of course vary from compound to compound as would be expected by those skilled in the art but all of the compounds tested to date show anto-inflammatory and/or C.N.S. activity to a greater or lesser extent.

The results obtained in the aforementioned tests for certain representative compounds of the present invention are set forth in the following Table. In the case of the rat paw volume test, most of the results are expressed either as the calculated p.o. dose (AED) which has the same effect in the test as 64 mg/kg body weight of aspirin or as calculated p.o. base dose (RD_{40}) which inhibits the induced oedema by 40%. Some results however are expressed as percentage inhibition of oedema at a stated p.o. dose.

The results for the amphetamine test are expressed as the degree of potentiation of amphetamine stereotypy (POT) measured on a scale of 0 to ++ and the degree of prolongation of stereotypy (PROL) measured on a scale of 0 to +++ at the stated dose.

The initials "IA" and "NT" are used in the table to mean respectively inactive at the stated dose and not tested or result not recorded.

Those compounds marked "HM" were in the form of the hydrogen maleate; those marked "HCl" were in the form of the hydrochloride and that marked "HO" was in the form of its hydrogen oxalate.

TABLE

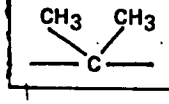
$-Y_1\ Y_2-$	R_1-N-R_2	$(R_3)_n$	$(R_4)_m$	R_5	Amphetamine POT/PROL	Rat Paw Volume	No.
-H H-	CH_3-N-CH_3	n=o	m=o	H	0/+++ 20 p.o.	AED 27 p.o.	1 HM
-H H-	CH_3-N-CH_3	7-Cl	4' Cl	H	NT/+ 100 i.p.	1A 64 p.o.	2 HM
-H H-	CH_3-N-CH_3	$7-CH_3O$	$4'-CH_30$	H	0/+ 100 i.p.	NT	3 HM
$-CH_3$ H-	CH_3-N-CH_3	n=o	$2'CH_3$	H	+/++ 50 p.o.	1A 64 p.o.	4 HCl
Bond	CH_3-N-CH_3	n=o	m=o	H	0/0 100 i.p.	1.A. 64 p.o.	5
-O-	CH_3-N-CH_3	n=o	m=o	H	+/0 50. p.o.	1.A. 64 p.o.	6
-S-	CH_3-N-CH_3	n=o	m=o	H	0/+++ 45 p.o.	1.A. 64 p.o.	7
$-CH_2\ CH_2-$	CH_3-N-CH_3	n=o	m=o	H	+/+++ 50 p.o.	RD_{40} 78 p.o.	8 HM
	CH_3-N-CH_3	n=o	m=o	H	0/+++ 12.5 p.o.	RD_{40} 41 p.o.	9 HO

TABLE (Continued)

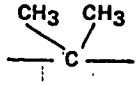
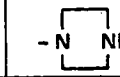
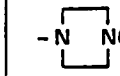
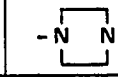
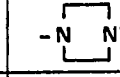
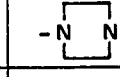
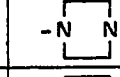
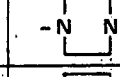
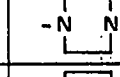
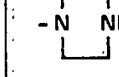
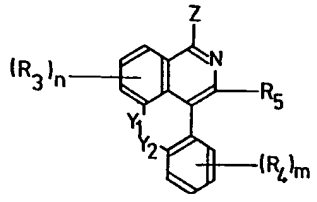
$-CH_2O-$	CH_3-N-CH_3	n = o	m = o	H	+/+ 50 p.o.	NT	10
$-OCH_2-$	CH_3-N-CH_3	n = o	m = o	H	+/+++ 45 p.o.	NT	11 HM
–H H–	CH_3-N-H	n = o	m = o	H	+/+++ 100 p.o.	1A 64 p.o.	12
Bond	CH_3-N-H	n = o	m = o	H	+/+++ 45 p.o.	1A 64 p.o.	13
-O-	CH_3-N-H	n = o	m = o	H	+/+ 50 p.o.	1A 64 p.o.	14
-S-	CH_3-N-H	n = o	m = o	H	+/+++ 50 p.o.	1A 64 p.o.	15
$-CH_2CH_2-$	CH_3-N-H	n = o	m = o	H	+/+++ 10 p.o.	17% 64 p.o.	16
	CH_3-N-H	n = o	m = o	H	++/++ 12.5 p.o.	50% 64 p.o.	17
$-CH_2O-$	CH_3-N-H	n = o	m = o	H	0/0 50 p.o.	NT	18 HM
$-OCH_2-$	CH_3-N-H	n = o	m = o	H	+/+++ 15 p.o.	NT	19

TABLE (Continued)

-H H-		n = o	m = o	H	0/+++ 20 i.p.	AED 13 p.o.	20 HM
-H H-		n = o	m = o	H	+/+++ 50 p.o.	RD_{40} 57 p.o.	21
-H H-		n = o	m = o	H	0/0 100 i.p.	AED 19 p.o.	22
-H H-		7 Cl	4'Cl	H	0/0 100 i.p.	AED 51 p.o.	23
-H H-		7 Cl	4'Cl	H	0/0 50 p.o.	1A 64 p.o.	24
-H H-		7 CH_3O	4'CH_3O	H	NT/+ 20 i.p.	AED 13 p.o.	25
-H H-		7 CH_3O	4'CH_3O	H	+/+ 50 p.o.	AED 144 p.o.	26
Bond		n = o	m = o	H	+/+ 50 p.o.	NT	27
$-CH_2CH_2-$		n = o	m = o	H	0/+ 50 p.o.	31% 64 p.o.	28 HM

The compounds of the present invention can be prepared by treating in manner known *per se* a corresponding 1-Z-substituted 4-phenyl-isoquinoline of general formula III:—



III

wherein Z represents an electron-withdrawing leaving group and n, m, R_3, R_4, R_5, Y_1 and Y_2 are as defined in connection with formula II and the amine reactant will be of the formula IV

IV

wherein R and R_2 are as defined in connection with formula II.

Suitably, Z will be halogen, especially chlorine or alkyl- or phenylthio, -sulphinyl or -sulphonyl.

The reaction may be carried out in the presence or absence of a solvent and/or catalyst such as copper or cuprous salts and normally will be carried out at elevated temperatures. If necessary or desired the reaction may be carried out under pressure. When a solvent is used at atmospheric pressure, the reaction is conveniently carried out at the reflux temperature of the reaction mixture. Reaction times may vary from 1 to 24 hours depending on the reaction conditions. When a solvent is used, suitable solvents include benzene, chloroform, toluene, acetone, dioxan, dimethylformamide and dimethylsulphoxide.

The process may be employed to prepare all of the compounds of the present invention although in some cases direct formation of a particular compound from the corresponding 1-Z-substituted 4 phenyl isoquinoline may not be possible. However, it will be readily apparent to those skilled in the art that those compounds which cannot be prepared directly by the said reaction may be obtained by methods known *per se* from related 1-amino-4-phenylisoquinolines having basic formula II which can be prepared directly. In other cases, it may be desirable for a substituent in a compound prepared according to the foregoing process to be converted to another substituent to provide the desired compound. These conversion are carried out by methods well known *per se*. Thus, for example, a hydroxyalkyl substituent may be converted to a halogenoalkyl substituent by reaction with a halogenating agent such as thionyl chloride or phosphorus tribromide in the presence of an inert solvent such as chloroform. Similarly, an unsubstituted imino group in, for example a piperazinyl group, may be alkylated using conventional means such as by reaction with an alkylating agent for example an alkyl halide.

The compounds produced by the foregoing process may be isolated either *per se* or as acid addition salts or quaternary ammonium derivatives thereof.

The acid addition salts are preferably the pharmaceutically acceptable, non-toxic addition salts with suitable acids, such as those with inorganic acids, for example hydrochloric, hydrobromic, nitric, sulphuric or phosphoric acids, or with organic acids, such as organic carboxylic acids, for example, glycollic, maleic, hydroxymaleic, malic, tartaric, citric, salicylic, *o*-acetyloxybenzoic, nicotinic or isonicotinic, or organic sulphonic acids for example methane sulphonic, ethane sulphonic, 2-hydroxyethane-sulphonic, toluene-*p*-sulphonic, or naphthalene-2-sulphonic acids. Apart from pharmaceutically acceptable acid addition salts, other salts are also included within the scope of acid addition salts, such as for example, those with picric acid; they may serve as intermediates in the purification of the compounds or in the preparation of other, for example, pharmaceutically acceptable, acid addition salts, or are useful for identification, characterisation or purification of the bases.

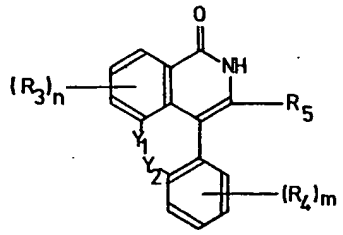
A resulting acid addition salt may be converted into the free compound according to known methods, for example, by treating it with a base, such as with a metal hydroxide or alkoxide, for example an alkali or alkaline earth metal hydroxide, for

example, lithium hydroxide, sodium hydroxide, potassium hydroxide or calcium hydroxide; with a metal carbonate, such as an alkali metal or an alkaline earth metal carbonate or hydrogen carbonate, for example, sodium, potassium or calcium carbonate or hydrogen carbonate; with ammonia; or with a hydroxyl ion exchange preparation, or with any other suitable reagent.

A resulting acid addition salt may also be converted into another acid addition salt according to known methods; for example, a salt with an inorganic acid may be treated with a metal salt, for example a sodium, barium or silver salt, or an acid in a suitable diluent, in which a resulting inorganic salt is insoluble and is thus removed from the reaction medium. An acid addition salt may also be converted into another acid addition salt by treatment with an anion exchange preparation.

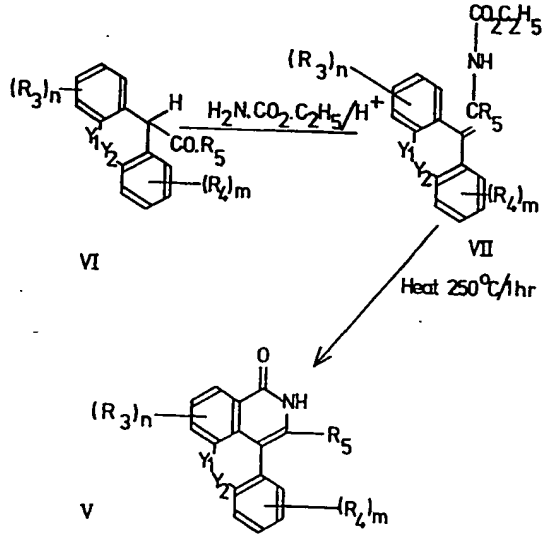
Quaternary ammonium derivatives of the compounds of this invention are particularly those formed by reaction with C_1—C_6 alkyl halides, for example, methyl, ethyl, or propyl chloride, bromide or iodide; di-C_1—C_6 alkyl sulphates, for example, dimethyl or diethyl sulphate; C_1—C_6 alkyl C_1—C_6 alkane sulphonates for example, methyl or ethyl methane sulphonate or ethane sulphonate; C_1—C_6 alkyl aryl sulphonates, for example methyl or ethyl *p*-toluene sulphonates; and phenyl-lower alkyl halides, for example benzyl or phenethyl chloride, bromide or iodide. Also included are the quaternary ammonium hydroxides and the quaternary ammonium compounds having as anions those of other inorganic or organic acids, for example those of the acids used for the preparation of the previously-mentioned acid addition salts.

The 1-Z-substituted-4-phenyl isoquinoline reactants may be obtained in manner known *per se*, for example by refluxing with $POCl_3$, from the corresponding 4-phenyl isoquinolones of general formula V

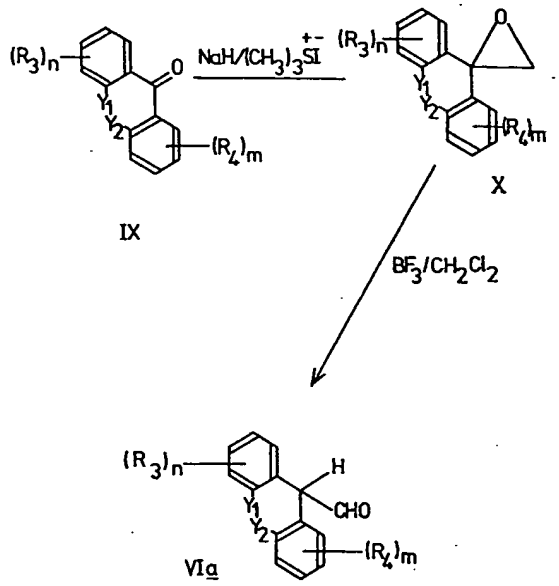


V

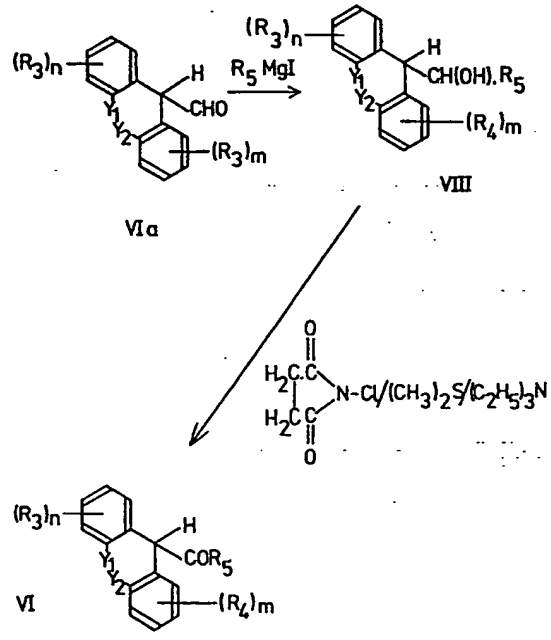
The 4-phenyl isoquinolone reactants can be obtained in manner known *per se*, for example as described in Arch. Pharm. 1963, *296*, 445 and Arch. Pharm. 1964, *297*, 488, from the corresponding diphenyl acetaldehyde or alkanone. The reaction sequence can be as follows:—



The diphenyl acetaldehyde reactant can be obtained by, for example, the method described in Canad. J. Chem. 1969, *47*, 4327 from the corresponding benzophenone. Where R_3 represents H, the reaction sequence can be as follows:—



The diphenyl alkanones can be prepared from the said diphenyl-acetaldehydes by, for example, addition of an alkyl magnesium iodide or bromide at room temperature in the presence of a non-polar organic solvent such as diethyl ether, heating the resultant mixture at reflux temperature to form the corresponding diphenyl alkanol, and then oxidation by, for example, the method disclosed in J. Amer. Chem. Soc. 1972, *94*, 7586. The reaction sequence can be as follows:—



In the composition aspect of the invention there are provided pharmaceutical formulations in which form the active compounds of the invention will normally be utilized. Such formulations are prepared in a manner well known *per se* in the pharmaceutical art and usually comprise at least one active compound of the invention in admixture or otherwise in association with a pharmaceutically acceptable carrier therefor. For making these formulations the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed or encapsulated in a capsule, sachet, cachet, paper or other container. A carrier or diluent may be a solid, semi-solid or liquid material which serves as a vehicle, excipient or medium for the active ingredient. Some examples of such diluents or carriers are lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, liquid paraffin, cocoa butter, oil or theobroma, alginates, tragacanth, gelatin, syrup B.P., methyl cellulose, polyoxyethylene sorbitan monolaurate, methyl- and propyl-hydroxybenzoate, talc, magnesium or mineral oil.

The formulations of the invention may be adapted for enteral or parenteral use and may be administered to a subject requiring treatment, for example an animal suffering an inflammatory condition, in the form of tablets, capsules, suppositories, solutions, suspensions or the like. The dosage required for the treatment of any animal will usually fall within the range of 0.01 to 250 mg/kg. For example in the treatment of adult humans, each dosage of active ingredient is expected to be from 0.01 to 15 mg/kg, whereas in the treatment of test animals such as mice and rabbits a dosage of 10 to 200 mg/kg may be used. The formulations of the invention may therefore be provided in dosage unit form, preferably each dosage unit containing from 1 to 1000 mg., more advantageously from 5 to 500 mg., and most preferably from 10 to 250 mg of the active ingredient of the invention.

The following Examples will further illustrate the preparation of the novel compounds of this invention. All temperatures are given in degrees Centigrade.

Example 1.

(a) 10,11 - Dihydro - spiro[5H - dibenzo[a,d]cycloheptene - 5,2' - oxirane] (see Formula X).

Dry dimethylsulphoxide (300 ml) and dibenzo[a,d]suberone (see Formula IX) (20.8 g) were added to petrol-washed 50% sodium hydride/oil (5 g) and the mixture stirred under a nitrogen atmosphere for 10 minutes. Trimethylsulphonium iodide (30 g 1.5 moles) was added and stirring continued for a further three and a half hours. The reaction mixture was poured into water (2000 ml) containing NaCl, and the precipitated product filtered off, washed with water, and dissolved in ether. The ether solution was dried ($MgSO_4$) and concentrated to give the product as a white solid (21.1 g, 96%).

(b) 5 - Formyl - 10,11 - dihydro - 5H - dibenzo[a,d]cycloheptene (see Formula VI a).

Boron trifluoride-dimethyletherate (5 ml) was added to a solution of the above epoxide (21.2 g) in dry methylene chloride (300 ml) and the mixture stirred at room temperature for 2 hours. The solution was washed cautiously with 10% $NaCHO_2$ (300 ml), and water, dried ($MgSO_4$) and concentrated to give the product as an oil (20.8 g, 98%) which crystallised.

(c) Ethyl(10,11 - dihydro - dibenzo[a,d]cyclohept - 5 - ylidenemethyl) - carbamate (see Formula VII).

A solution of the above aldehyde (20.8 g), urethane (8.35 g, 1 mole) and conc. H_2SO_4 (5 drops) in toluene (200 ml) was heated under reflux in a Dean and Stark apparatus for 2 hours. During this time water (1.6 ml, 95 %) was collected. The cooled reaction mixture was washed with dilute $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated to give the product as an oil (27.5 g, 100%).

(d) 7,8 - Dihydro - benzo[1,2]cyclohepta[3,4,5 - de]isoquinolone (see Formula V).

A solution of the above carbamate (27.5 g) in diphenyl ether (200 ml) was heated to reflux (256° internal) and maintained for 1 hour. The cooled reaction mixture was diluted with 60—80 petroleum-ether (300 ml) and the crystalline product filtered off, washed with 60—80 petroleum ether and dried. Yield 20.6 g (89%).

(e) 3 - Chloro - 7,8 - dihydro - benzo[1,2]cyclohepta[3,4,5 - de]isoquinoline hydrogen maleate (see Formula III).

A solution of the above isoquinolone (13.0 g) in phosphorus oxychloride (100 ml) was heated under reflux for one and three-quarter hours. The cooled and concentrated reaction mixture was taken up in chloroform and poured into an ice/conc. ammonia mixture. The chloroform layer was separated, washed with water, dried ($MgSO_4$) and concentrated to give the product as an oil (13.8 g, 99%) which crystallised.

(f) 3 - Dimethylamino - 7,8 - dihydro - benzo[1,2]cyclohepta[3,4,5 - de] isoquinoline hydrogen maleate (see Formula II).

A solution of the above chloro-compound (6.6 g) in 33% dimethylamine/ethanol (250 ml) was heated under reflux for 24 hours. The cooled and concentrated reaction mixture was dissolved in industrial methylated spirits and poured into water (800 ml) containing 2*N* NaOH (12.4 ml). The resulting oil was extracted with ether, and the extract separated, washed with water, dried ($MgSO_4$) and concentrated to give the crude product free base as a red oil (6.9 g, 100%). A solution of maleic acid (2.9 g) in methanol was added to a solution of the base (6.9 g) in industrial methylated spirits and concentrated to give the crude salt which was recrystallised from acetone. Yield 7.4 g (75.6%) m.p. 157—9.

Analysis

	C	H	N
Found	70.8	5.8	7.3
Required	70.8	5.6	7.2

Example 2.

(a) 9 - (1 - Hydroxyethyl) - xanthene (see Formula VIII).

A solution of methyl iodide (11.6 ml) in dry ether (80 ml) was added to a stirred suspension of magnesium turnings (4.5 g) in dry ether (20 ml) at such a rate to maintain gentle reflux. 9-Formyl-xanthene (31.4 g) in dry ether (150 ml) was added over 30 mins. and the reaction mixture heated under reflux for one and a half hours. 2*N*HCl (100 ml) was added dropwise to the cooled mixture, the liquors filtered and the ether layer separated, washed with water, dried ($MgSO_4$) and concentrated to give the product as an oil (33.7 g).

(b) 9 - Acetyl xanthene (see Formula VI).

Dimethyl sulphide (12.5 ml) was added to a suspension of N-chloro-succinimide (21.9 g) in dry toluene (300 ml) stirred under N_2 and the mixture cooled to −25° (internal). A solution of the above alcohol (33.7 g) in dry toluene (150 ml) was added dropwise, maintaining the temperature at below −20° C, and stirring continued at this temperature for 2 hours. A solution of tri-ethylamine (24 ml) in dry toluene (75 ml) was added dropwise and the temperature allowed to rise to room temperature. The solution was washed with very dilute HCl, water, 5% $NaHCO_3$, and water, dried ($MgSO_4$), and concentrated to give the crude product (34.3 g).

(c) Ethyl N - (1 - xanthylidene - ethyl) - carbamate (see Formula VII).

A solution of the above ketone (34.3 g), urethane (13.6) and conc. H_2SO_4 (6 drops) in toluene (270 ml) was heated under reflux in a Dean and Stark apparatus for 48 hours. The cooled reaction mixture was washed with dilute $NaHCO_3$ and water, dried ($MgSO_4$) and concentrated to give the crude product as an oil (44.6 g).

(d) 1 - Methyl - [1] - benzopyrano[4,3,2 - de]isoquinolone (see Formula V).

A solution of the above carbamate (44.6 g) in diphenyl ether (200 ml) was heated to reflux (256° internal) and maintained for 1 hour. The cooled reaction mixture was diluted with 60—80 petroleum ether (500 ml) and the precipitated product filtered off, washed with 40—60 petroleum ether and dried. Yield 6.5 g.

(e) 1 - Methyl - 3 - chloro - [1] - benzopyrano[4,3,2 - de]isoquinoline (see Formula III).

The above isoquinolone (6.5 g) was converted into the chloroisoquinoline using $POCl_3$ (30 ml) in the manner described in stage (e) of Example 1. Yield 6.5 g.

(f) 1 - Methyl - 3 - dimethylamino - [1] - benzopyrano[4,3,2 - de]isoquinoline hydrogen maleate (see Formula II).

A solution of the above chloro-isoquinoline (6.4 g) in 33% dimethylamine/ethanol (250 ml) was heated under reflux for 24 hours. The cooled and concentrated reaction mixture was taken up in industrial methylated spirits and poured into water (500 ml) containing 2*N* NaOH (12.0 ml). The resulting oil was extracted with ether, and the ether layer washed with water (2x), dried ($MgSO_4$) and concentrated to give the crude base (6.1 g). A solution of maleic acid (2.6 g) in industrial methylated spirits (20 ml) was added to a solution of the base (6.1 g) in industrial methylated spirits (40 ml). The crystalline product was collected and recrystallised from industrial methylated spirits. Yield 4.5 g; m.p. 133.4°.

Analysis

	C	H	N
Found	67.2	5.4	7.2
Required	67.4	5.1	7.1

The following compounds are prepared by similar processes to those described in Examples 1 and 2. The numbers appearing in brackets after some of the compounds refer to the number of that compound in the preceding Table of this Specification.

1 - (4 - β - hydroxyethylpiperazin - 1 - yl) - 4 - phenyl - isoquinoline, m.p. 183—5°, (22);
4 - phenyl - 1 - (piperazin - 1 - yl) - isoquinoline hydrogen maleate, m.p. 198—9°, (20);
1 - (4 - β - hydroxyethylpiperazin - 1 - yl) - 4 - (4 - methoxyphenyl) - 7 - methoxy-isoquinoline, m.p. 123—4°, (26);
1 - (piperazin - 1 - yl) - 4 - (4 - methoxyphenyl) - 7 - methoxy - isoquinoline, m.p. 127—8°, (25);
1 - (4 - β - hydroxyethylpiperazin - 1 -yl) - 4 - (4 - chlorophenyl) - 7 - chloro isoquinoline, m.p. 162—3°, (24);
1 - (piperazin - 1 - yl) - 4 - (4 - chlorophenyl) - 7 - chloro - isoquinoline, m.p. 152—3°, (23);
1 - dimethylamino - 4 - phenyl - isoquinoline hydrogen maleate, m.p. 160—1°, (1);
1 - dimethylamino - 4 - (4 - chlorophenyl) - 7 - chloro -isoquinoline hydrogen maleate, m.p. 179—181°, (2);
1 - dimethylamino - 7 - methoxy - 4 - (4 - methoxyphenyl) - isoquinoline hydrogen maleate, m.p. 136—8°, (3);
1 - dimethylamino - indeno[1,2,3 - de]isoquinoline, m.p. 141—3°, (5);
11(4 - β - hydroxyethylpiperazin - 1 - yl) - indeno[1,2,3 - de]isoquinoline, m.p. 152—4°, (27);
1 - methylated - 4 - phenyl - isoquinoline, m.p. 155—6°, (12);
3 - methylamino - 7,8 - dihydro - benzo[1,2]cyclohepta[3,4,5 - de]isoquinoline, m.p. 156-8° (16);
1 - (4 - methylpiperazin - 1 - yl) - 4 - phenyl - isoquinoline, m.p. 143—5° (21);
3 - (piperazin - 1 yl) - 7,8 - dihydro - benzo[1,2]cyclohepta[3,4, 5- de]isoquinoline hydrogen maleate, m.p. 198—9°, (28);
3 - methylamino - indeno[1,2,3 - de]isoquinoline, m.p. 167—9°, (13);
1 - dimethylamino - 4 - (o - tolyl) - 5 - methyl - isoquinoline hydrochloride, m.p. 211—2° (4);
3 - dimethylamino - [1]benzopyrano[4,3,2 - de]isoquinoline, m.p. 156—7°, (6);
3 - methylamino - [1] - benzopyrano[4,3,2 - de]isoquinoline, m.p. 257—9° (14);
3 - dimethylamino - [1]]benzothiopyranol[4,3,2 - de]isoquinoline, m.p. 111—2°, (7);
3 - methylamino - [1]benzothiopyrano[4,3,2 - de]isoquinoline, m.p. 179—81°, (15);
3 - dimethyl - 7,7 - dimethyl - 7H - dibenz[de,h]isoquinoline hydrogen oxalate, m.p. 191—3°, (9);
3 - methylamino - 7,7 - dimethyl - 7H - dibenz[de,h]isoquinoline, m.p. 164—5°, (17);
3 - dimethylamino - 7H - [1] - benzoxepino[5,4,3 - de]isoquinoline, m.p. 104—6°, (10);
3 - dimethylamino - 8H - [2] - benzoxepino[5,4,3 - de]isoquinoline hydrogen maleate, m.p. 179—80°, (11);
3 - methylamino - 7H - [1]benzoxepino[5,4,3 - de]isoquinoline hydrogen maleate, m.p. 208°, (18);

3 - methylamino - 8H - [2] - benzoxepino[5,4,3 - de]isoquinone, m.p. 171°, (19);
1 - dimethylamino - 3 - methyl - 4 - phenyl - isoquinoline, m.p. 203—5°;
1 - methyl - 3 - dimethylamino - [1]benzopyrano[4,3,2 - de]isoquinoline hydrogen maleate, m.p. 133—4°;
1 - dimethylamino - 4 - (m - trifluoromethylphenyl) - isoquinoline;
3 - dimethylamino - 10 - trifluoromethyl - [1] - benzopyrano[4,3,2 - de] isoquinoline; and
3 - dimethylamino - benzo[1,2]cyclohepta[3,4,5 - de]isoquinoline.

In the following Examples relating to pharmaceutical compositions, the term "medicament" is used to indicate the compound 1 - dimethylamino - 4 - phenyl-isoquinoline. This compound may be replaced in these compositions by any other anti-inflammatory compound of the invention, for example by 3 - dimethylamino - 7,8-dihydro - benzo[1,2]cyclohepta[3,4,5 - de]isoquinoline. Adjustments in the amount of medicament may be necessary or desirable depending upon the degree of activity of the medicament as is well known in the art.

Example 3—Tablet formulation.

	mg/tablet
Medicament	15
Lactose	86
Maize Starch (dried)	45.5
Gelatin	2.5
Magnesium stearate	1.0

The medicament is powdered and then passed through a B.S. No. 100 sieve and mixed well with the lactose and 30 mg of the maize starch, both passed through a B.S. No. 44 sieve.

The mixed powders are massed with a warm gelatin solution prepared by stirring the gelatin in water and heating to form a 10% w/w solution. The mass is granulated by passing through a B.S. No. 12 sieve and the moist granules dried at 40°.

The dried granules are re-granulated by passing through a B.S. No. 14 sieve and the balance of the starch sieved 44 mesh and the magnesium stearate sieved 60 mesh are added and thoroughly mixed.

The granulates are compressed to produce tablets each weighting 150 mg.

Example 4—Tablet formulation.

	mg/tablet
Medicament	100
Lactose	39
Maize starch (dried)	80
Gelatin	4.0
Magnesium stearate	2.0

The method of preparation is identical with that of Example 3 except that 60 mg of starch is used in the granulation process and 20 mg during tabletting.

Example 5—Capsule formulation.

	mg/capsule
Medicament	250
Lactose	150

The medicament and lactose are passed through a No. 44 B.S. sieve and the powders well mixed together before filling into hard gelatin capsules of suitable size, so that each capsule contains 400 mg of mixed powders.

Example 6—Suppositories.

	mg/suppository
Medicament	50
Oil of Theobroma	950

The medicament is powdered and passed through a B.S. No. 100 sieve and

triturated with molten oil of Theobroma at 45° C to form a smooth suspension. The mixture is well stirred and poured into moulds, each of nominal 1G capacity, to produce suppositories.

Example 7—Cachets.

	mg/cachet
Medicament	100
Lactose	400

The medicament is passed through a B.S. No. 40 mesh sieve, mixed with lactose previously sieved 44 mesh and filled into cachets of suitable size so that each contains 500 mg.

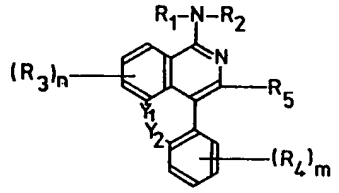
Example 8—Intramuscular Injection (suspension in aqueous vehicle).

Medicament	10 mg
Sodium Citrate	5.7 mg
Sodium carboxymethylcellulose (low viscosity grade)	2.0 mg
Methyl para-hydroxybenzoate	1.5 mg
Propyl para-hydroxybenzoate	0.2 mg
Water for Injection	to 1.0 ml

The sodium citrate and sodium carboxymethylcellulose are mixed with sufficient water for injection at 80° C. The mixture is cooled to 50° C and the methyl and propyl para-hydroxybenzoate added followed by the medicament previously milled and sieved 300 mesh. When cool the injection is made up to volume and sterilized by heating in an autoclave.

WHAT WE CLAIM IS:—

1. 1 - Amino - 4 - phenyl isoquinolines of formula II:—



II

wherein R_1 and R_2 independently represent hydrogen or C_1—C_{12} alkyl, or R_1 and R_2 together with the amino nitrogen atom represent a piperazinyl ring optionally substituted by C_1—C_{12} alkyl or C_1—C_{12} hydroxyalkyl;

n represents zero or an integer not exceeding 3;

m represents zero or an integer not exceeding 4,

R_3 and R_4 independently represent C_1—C_{12} alkyl optionally substituted by one or more halogens; C_1—C_{12} alkoxy or halogen;

R_5 represents hydrogen or C_1—C_{12} alkyl; and

Y_1 and Y_2 independently represent hydrogen, C_1—C_{12} alkyl, C_1—C_{12} alkylthio, C_1—C_{12} alkoxy or Y_1 and Y_2 together represent a single valency bond, an oxygen or sulphur atom or an alkylene radical optionally containing one or more oxygen or sulphur atoms and joining the 4-phenyl group to the isoquinoline nucleus in a chain of 1 to 3 atoms.

2. Compounds as claimed in Claim 1 wherein:

R_1 and R_2 independently represent hydrogen or C_1—C_4 alkyl, or R_1 and R_2 together with the amino nitrogen atom represent a piperazinyl ring optionally substituted by C_1—C_4 alkyl or C_1—C_4 hydroxyalkyl;

n represents zero or an integer not exceeding 3;

m represents zero or an integer not exceeding 4;

R_3 and R_4 independently represent C_1—C_4 alkyl optionally substituted by one or more halogens; C_1—C_4 alkoxy or halogen;

R_5 represents hydrogen or C_1—C_4 alkyl; and

Y_1 and Y_2 independently represent hydrogen, C_1—C_4 alkyl, C_1—C_4 alkylthio,

C_1—C_4 alkoxy or Y_1 and Y_2 together represent a single valency bond, an oxygen or sulphur atom or an alkylene radical optionally containing one or more oxygen or sulphur atoms and joining the 4-phenyl group to the isoquinoline nucleus in a chain of 1 to 3 atoms.

3. Compounds as claimed in Claim 1 or Claim 2 wherein *n* and *m* independently represent 0 or 1.

4. Compounds as claimed in any one of the preceding Claims wherein R_1 and R_2 are selected from hydrogen, methyl, and those divalent radicals which together with the amino nitrogen atom will form a 4-X-substituted piperazin-1-yl group wherein X represents hydrogen, C_1—C_4 alkyl or C_1—C_4 hydroxyalkyl.

5. Compounds as claimed in any one of the preceding Claims wherein R_3 and R_4 are selected from methyl, trifluoromethyl, methoxy and chlorine.

6. Compound as claimed in any one of the preceding Claims wherein R_5 is hydrogen or methyl.

7. Compounds as claimed in any one of the preceding Claims wherein Y_1 and Y_2 are selected from hydrogen, methyl, methoxy, methylthio and, when Y_1 and Y_2 together represent an alkylene group, ethylene, methyleneoxy, methylenethio and isopropylidene.

8. Compounds as claimed in any one of the preceding Claims wherein R_1 represents methyl and R_2 represents hydrogen or methyl.

9. Compounds as claimed in Claim 8, wherein R_3 and R_4 independently represent chlorine or methoxy or *m* and/or *n* is zero.

10. 3 - Dimethylamino - 7,8 - dihydro - benzo[1,2]cyclohepta[3,4,5 - de] isoquinoline and acid addition salts thereof.

11. 1 - Methyl - 3 - dimethylamino - [1] - benzopyrano-4,3,2 - de] - isoquinoline and acid addition salts thereof.

12. 1 - (4 - β - Hydroxyethylpiperazin - 1 - yl) - 4 - phenyl - isoquinoline and acid addition salts thereof.

13. 4 - Phenyl - 1 - (piperazin - 1 - yl) - isoquinoline and acid addition salts thereof.

14. 1 - (4 - β - Hydroxyethylpiperazin - 1 - yl) - 4 - (4 - methoxyphenyl) - 7-methoxy - isoquinoline and acid addition salts thereof.

15. 1 - (Piperazin - 1 - yl) - 4 - (4 - methoxyphenyl) - 7 - methoxy - isoquinoline and acid addition salts thereof.

16. 1 - (4 - β - Hydroxyethylpiperazin - 1 - yl) - 4 - (4 - chlorophenyl) - 7-chloro - isoquinoline and acid addition salts thereof.

17. 1 - (Piperazin - 1 - yl) - 4 - (4 - chlorophenyl) - 7 - chloro - isoquinoline and acid addition salts thereof.

18. 1 - Dimethylamino - 4 - phenyl - isoquinoline and acid addition salts thereof.

19. 1 - Dimethylamino - 4 - (4 - chlorophenyl) - 7 - chloro - isoquinoline and acid addition salts thereof.

20. 1 - Dimethylamino - 7 - methoxy - 4 - (4 - methoxyphenyl) - isoquinoline and acid addition salts thereof.

21. 1 Dimethylamino - indeno[1,2,3 - de]isoquinoline and acid addition salts thereof.

22. 1 - (4 - β - Hydroxyethylpiperazin - 1 - yl) - indeno[1,2,3 - de] - isoquinoline and acid addition salts thereof.

23. 1 - Methylamino - 4 - phenyl - isoquinoline and acid addition salts thereof.

24. 3 - Methylamino - 7,8 - dihydro - benzo[1,2]cyclohepta[3,4,5 - de]isoquinoline and acid addition salts thereof.

25. 1 - (4 - Methylpiperazin - 1 - yl) - 4 - phenyl - isoquinoline and acid addition salts thereof.

26. 3 - (Piperazin - 1 - yl) - 7,8 - dihydro - benzo[1,2]cyclohepta[3,4,5 - de]-isoquinoline and acid addition salts thereof.

27. 3 - Methylamino - indeno[1,2,3 - de]isoquinoline and acid addition salts thereof.

28. 1 - Dimethylamino - 4 - (o - tolyl) - 5 - methyl - isoquinoline and acid addition salts thereof.

29. 3 - Dimethylamino - [1] - benzopyrano [4,3,2 - de]isoquinoline and acid addition salts thereof.

30. 3 - Methylamino - [1] - benzopyrano[4,3,2 - de]isoquinoline and acid addition salts thereof.

31. 3 - Dimethylamino - [1] - benzothiopyrano[4,3,2 - de] - isoquinoline and acid addition salts thereof.

32. 3 - Methylamino - [1] - benzothiopyrano[4,3,2 - de]isoquinoline and acid addition salts thereof.

33. 3 - Dimethylamino - 7,7 - dimethyl - 7H - dibenz[de,h]isoquinoline and acid addition salts thereof.

34. 3 - Methylamino - 7,7 - dimethyl - 7H - dibenz[de,h] isoquinoline and acid addition salts thereof.

35. 3 - Dimethylamino - 7H - [1] - benzoxepino[5,4,3 - de]isoquinoline and acid addition salts thereof.

36. 3 - Dimethylamino - 8H - [2] - benzoxepino[5,4,3 - de]isoquinoline and acid addition salts thereof.

37. 3 - Methylamino - 7H - [1]benzoxepino[5,4,3 - de]isoquinoline and acid addition salts thereof.

38. 3 - Methylamino - 8H - [2] - benzoxepino[5,4,3 - de]isoquinoline and acid addition salts thereof.

39. 1 - Dimethylamino - 3 - methyl - 4 - phenyl - isoquinoline and acid addition salts thereof.

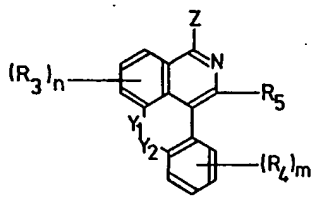
40. 1 - Methyl - 3 - dimethylamino - [1]benzopyrano[4,3,2 - de] - isoquinoline and acid addition salts thereof.

41. 1 - Dimethylamino - 4 - (m - trifluoromethylphenyl) - isoquinoline and acid addition salts thereof.

42. 3 - Dimethylamino - 10 - trifluoromethyl - [1] - benzopyrano - [4,3,2 - de]-isoquinoline and acid addition salts thereof.

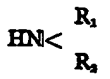
43. 3 - Dimethylamino - benzo[1,2]cyclohepta[3,4,5 - de] - isoquinoline and acid addition salts thereof.

44. A method of preparing compounds as claimed in Claim 1, which comprises treating an isoquinoline reactant of general formula III:—



III

wherein Z represents an electron-withdrawing leaving group and n, m, R_3, R_4, R_5, Y_1 and Y_2 are as defined in Claim 1 with an amine reactant of the formula IV



IV

wherein R_1 and R_2 are as defined in Claim 1.

45. A method as claimed in Claim 44, wherein Z is halogen or alkyl- or phenyl-thio, -sulphinyl or -sulphonyl.

46. A method as claimed in Claim 44 and substantially as hereinbefore described in Example 1 or Example 2.

47. Pharmaceutical compositions comprising as an active ingredient a compound as claimed in any one of Claims 1 to 43 together with a pharmaceutically acceptable carrier.

48. Compositions as claimed in Claim 47 in dosage unit form.

49. Compositions as claimed in Claim 49 wherein each dosage unit contains from 1 to 1000 mg of the active compound.

50. Compositions as claimed in Claim 49 wherein each dosage unit contains from 5 to 500 mg of the active compound.

51. Compositions as claimed in Claim 50, wherein each dosage unit contains from 10 to 250 mg of the active compound.

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